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Problems in Diagnosing Scabies, a Global Disease in Human and Animal Populations

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INTRODUCTION

Background

Scabies is a common parasitic infection caused by the mite *Sarcoptes scabiei*. Infestations occur when the "itch" mite, *S. scabiei*, burrows into the skin and consumes host epidermis and sera. The predominant disease manifestations are mediated through inflammatory and allergy-like reactions to mite products, leading to intensely pruritic lesions. Scabies is a major global health problem in many indigenous and Third World communities. It causes outbreaks in nursing homes (99) and is recognized in those with human immunodeficiency virus and human T-cell leukemia virus type 1 infections (47, 48, 73, 97). Scabies is transmitted by skin-to-skin contact, as demonstrated in classical studies by Mellanby (79), who showed that direct person-to-person body contact was generally necessary for transmission of scabies. Thus, it is a disease of overcrowding and poverty rather than a reflection of poor hygiene (57). It has been estimated that 300 million people suffer from scabies infestation at any one time (102), although this number has been disputed (25). Scabies is an important disease of children, but it occurs in both sexes, at all ages, in all ethnic groups, and at all socioeconomic levels. Importantly, the associated mor-

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bidity is frequently underestimated. In addition to the discomfort caused by the intensely pruritic lesions, infestations often become secondarily infected, especially with group A streptococci and *Staphylococcus aureus.* Epidemic acute poststreptococcal glomerulonephritis (APSGN) is often associated with endemic scabies in the affected community (29, 96). Despite the availability of chemotherapy, repeated scabies infestations and the resultant recurrent pyoderma have now been identified as important cofactors in the extreme levels of renal and rheumatic heart disease observed in Aboriginal communities (30, 63, 112). Scabies is also a major problem among important livestock and companion animals, with, for example, approximately 25% of pigs in some areas of the United States experiencing scabietic mange, leading to major economic losses (22, 89). Moreover, many millions of wild animals worldwide suffer from sarcoptic mange. Even though this worldwide disease has been recognized throughout history, in the modern era there have been long interruptions and significant gaps in the research about scabies. Molecular studies of the parasite have been very limited, due to the generally low parasite burden and lack of an in vitro culture system. The first molecular studies of *Sarcoptes scabiei* var. *hominis* were enabled via the collection of large numbers of mites from the shed skin of crusted scabies patients in 1997 (107).

History

Scabies has been known to humankind since ancient times, with Aristotle (384 to 322 BC), the first person believed to have identified scabies mites, describing them as "lice in the flesh" and utilizing the term "akari." Subsequently, scabies has been mentioned by many different writers, including Arabic physician Abu el Hasan Ahmed el Tabari, around 970, Saint Hildegard (1098 to 1179), and the Moorish physician Avenzoar (1091 to 1162) (93). In 1687, Bonomo and Cestoni accurately described the cause of scabies in a letter (81). Their description recounting the parasitic nature, transmission, possible cures, and microscopic drawings of the mite and eggs of *S. scabiei* is believed to be the first mention of the parasitic theory of infectious diseases. Nevertheless, it was not until 1868, 2 centuries later, that the cause of scabies was established with the publication of a treatise by Hebra (19a, 52).

BIOLOGY

Classification

S. scabiei is an obligate ectoparasitic arthropod taxonomically grouped in the class Arachnida, subclass Acari, order Astigmata, and family Sarcoptidae (39). The members of the Astigmata are relatively slow-moving mites with thinly sclerotized integuments and no detectable spiracles or tracheal systems. Over 15 different varieties or strains have been described from various hosts, although morphologically they appear to be similar (38). However, cross-infestation experiments (10) and molecular epidemiology studies (106, 108) indicate clear physiological and genetic differences between host strains.

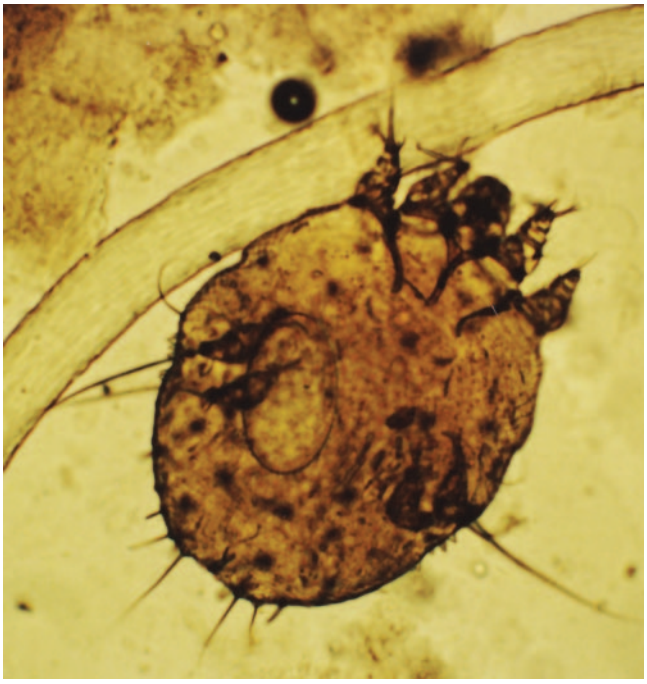

FIG. 1. Female scabies mite with egg, taken from skin scraping.

Life Cycle

The female mite burrows just under the surface of the skin and lays two to three eggs per day in the stratum corneum for up to 6 weeks at a time, resulting in raised papules on the skin's surface. However, it appears that fewer than 1% of the laid eggs develop into adult mites (78). Developmental instars include egg, larva, protonymph, and tritonymph (12). Adult mites emerge on the surface of the skin after approximately 2 weeks, and after mating, they reinfect the skin of the host or of another human. The male mite is reported to die after mating, although this has been disputed (1, 54).

Morphology

S. scabiei is creamy white with brown sclerotized legs and mouthparts (Fig. 1). The adult female is approximately 0.3 to 0.5 mm long by 0.3 mm wide, and the male is slightly smaller, around 0.25 mm long by 0.2 mm wide. Larvae have six legs, and nymphs and adults have eight legs, with stalked pulvilli (suckers) present on legs 1 and 2 of both the male and female adult mites, enabling them to grip the substrate. Additionally, mites bear spur-like claws, and they have six or seven pairs of spine-like projections on their dorsal surfaces. The adult male is distinguishable from the female by its smaller size, darker color, and the presence of stalked pulvilli on leg 4; leg 4 in the adult female ends in long setae.

Infectivity, Survival, and Transmission

Scabies transmission is mediated primarily by close, prolonged personal contact with an infected person and therefore is common among family members and often seen in institutional settings. Among adults, sexual contact is perhaps the

most important means of transmission. The probability of being infected is related to the number of mites on the infected person and the length of contact. Scabies is not readily transmitted by clothing, bed sheets, or other fomites (78), but this mode of transmission should be considered with cases of crusted (severe) scabies, due to the extreme mite burden. When the mite is dislodged from its host, it can survive for 24 to 36 h at room temperature with normal humidity (21°C and 40 to 80% relative humidity) and even longer at lower temperatures with high humidity (9). However, the mites' ability to infest the host decreases with increased time off the host. The sightless mite uses odor and thermal stimuli for active host taxis (3, 11).

EPIDEMIOLOGY

In many tropical and subtropical areas, such as Africa (85, 100), Egypt (53), Central and South America (56, 104), northern and central Australia (109), the Caribbean Islands (96), India (72, 84), and Southeast Asia (92), scabies is endemic. In industrialized countries, scabies is observed primarily in sporadic individual cases and institutional outbreaks (32, 36). Epidemiological studies indicate that the prevalence of scabies is not affected by sex, race, age, or socioeconomic status. The primary contributing factors in contracting scabies seem to be poverty and overcrowded living conditions (45, 109). Notwithstanding this, certain groups are more affected by the disease than others. Scabies is most commonly observed in the very young, followed by older children and young adults (1). In situations where scabies is endemic, this most likely reflects reduced immunity as well as increased exposure (27). Other age groups more commonly affected by scabies infestations include mothers of young children and the elderly in nursing homes. The latter cases are often related to index cases of crusted scabies in combination with compromised immune systems and possibly a decreased ability to kill the mites by scratching due to dementia and/or strokes. Lack of sensitization and/or reduced scratching is also believed to be the reason patients with paralysis or sensory neuropathy can develop localized crusting in affected areas (B. J. Currie and S. F. Walton, personal observation). It has yet to be established whether asymptomatic cases of scabies can occur and whether a history of infection with *S. scabiei* will cause long-term immunity.

Cyclical Pattern of Infection

Early accounts of the epidemiology of human scabies described large epidemics or pandemics of scabies. The principal peaks appear to coincide with major wars and occurred between 1919 and 1925, 1936 and 1949, and 1964 and 1979 (46). Because scabies is not a reportable disease, this may not be truly representative of its prevalence, as data are often based on variable recording methods and come from countries with widely varied social and physical environments. Furthermore, peak incidences of disease did not occur simultaneously in all countries (87). Herd immunity has been suggested as a reason for the possible cyclical nature of the disease, as it has been demonstrated that both people and animals with reinfestations have reduced parasitic burdens and some previously infected individuals can eliminate a second infestation (8, 78). However, this theory does not account for the endemicity of scabies in many tropical and subtropical communities (e.g., northern Australia, India, and South Africa) without any apparent fluctuations in overall incidence (84, 87, 109). Overcrowding and the continuous availability of new cohorts of susceptible young children may maintain the infection cycle in communities where scabies is endemic, whereas during war, the most likely reason for outbreaks is the crowding together of scabies-naïve adult populations (27). Of note, increases in scabies often run parallel to increases in the prevalence of other external arthropod parasites, e.g., head or body lice. Again, this is indicative of the role of the social environment in transmission (34).

Poverty, Overcrowding, and Poor Hygiene

The relationship between the prevalence of scabies and the relative levels of poverty, crowding, and hygiene within a community is complex. Evidence indicates that scabies is not influenced by hygiene practices or the availability of water. This can be observed in institutional outbreaks, where high standards of hygiene are observed (60, 88), and in coastal tropical communities with plentiful access to water and meticulous hygiene (69, 101). Furthermore, scabies is known to affect people from all socioeconomic levels, including affluent populations, if exposure occurs. Poverty and overcrowding, however, are often concomitant, and overcrowding is believed to have a significant effect on the spread of scabies, reflecting the fundamental role of physical contact in person-to-person transmission. Poverty also leads to other associated problems, such as poor nutritional status, which may in turn contribute to the immune status of the individual and the levels of disease within the community. Nutritional status has been reported as a significant risk factor in a scabies outbreak in an Indian village (84), and malnutrition may predispose individuals to crusted scabies (97).

Significance in Australian Indigenous Communities

Despite the availability of effective chemotherapy, scabies is still a major problem in many remote Aboriginal communities in Australia, relating primarily to levels of poverty and overcrowding (30). Carapetis et al. published prevalences for scabies of 25% in adults from these communities (21). Higher rates in schoolchildren were recorded, with prevalence rates of 30 to 65% (26). Nair et al. related a similar level of endemic scabies in an Indian village (84). Scabies is increasingly recognized as a major driving force of streptococcal pyoderma in children in these communities, underlying 50 to 70% of all skin infections. Group A streptococcus is responsible for the continuing outbreaks of APSGN and acute rheumatic fever reported in these communities, with rates of acute rheumatic fever and rheumatic heart disease among the highest in the world (29). Furthermore, scabies and skin infections in childhood have been linked with the extreme rates of end-stage renal failure in indigenous adults. Children with skin sores are five times more likely to develop APSGN during an epidemic, while the risk is doubled for those with scabies (65). Having had APSGN in childhood increases the risk of adult renal disease sixfold (112).

CLINICAL FEATURES

Ordinary Scabies

Clinical presentation with a primary infestation of scabies is reported to take place 4 to 6 weeks after infection. Presentation is with generalized itching, which is frequently reported to be more intense at night. Localization of the pruritic papules in human patients with scabies is classically in the webs of the fingers, the flexor aspects of the wrists, the extensor aspects of the elbows, the periumbilical skin, the buttocks, the ankles, the penis in males, and the periareolar region in females. The number of mites per patient is reported to be approximately 10 to 12, and with repeated infestations, this number reduces substantially (78). Although scabies infestation and total mite numbers in humans are usually self-limiting, spontaneous recovery from scabies in humans has been described to occur only with subsequent reinfestations (78). Depending on the extent and severity of the inflammatory response, the clinical appearance of scabies can be wide-ranging, but the classical clinical sign for the diagnosis of scabies is the burrow. The adult female, approximately 0.3 mm in length, makes the burrow as it digests and consumes the horny layer of the epidermis and the sera that seeps into the burrow from the dermis. Burrows present as serpiginous, grayish lines approximately 5 mm long, but often these are not detectable, especially in tropical locations (S. F. Walton and B. J. Currie, unpublished observations; D. Taplin, personal communication). An atypical appearance is frequently found in patients with long-standing infestations who may develop chronic excoriation and eczematization of the skin. Patients taking topical or oral steroids or who are immunosuppressed due to other diseases may also present uncharacteristically. In some situations, the rash and itch of scabies can persist for up to several weeks after curative treatment, possibly due to dead mites or mite products remaining within the skin layers. In a few cases, nodules can develop (nodular scabies), which can persist for several months after successful treatment. These firm, red-brown nodules are often extremely itchy and are commonly found in the groin, buttocks, and periumbilical area.

Reinfestation

With reinfestation, sensitization develops rapidly, and the associated lesions and pruritus are evident within 24 to 48 h.

Differential Diagnosis

The clinical signs and symptoms of scabies infestations can mimic many other skin conditions. These include bites from insects such as midges, fleas, and bedbugs; infections such as folliculitis, impetigo, tinea, and viral exanthema; eczema, contact dermatitis, and allergic reactions such as papular urticaria; and immunologically mediated diseases such as bullous pemphigoid and pityriasis rosea. Diagnosis can therefore be problematic.

Secondary Infection

Untreated scabies is often associated with pyoderma from secondary infection with group A streptococcus and *S. aureus*

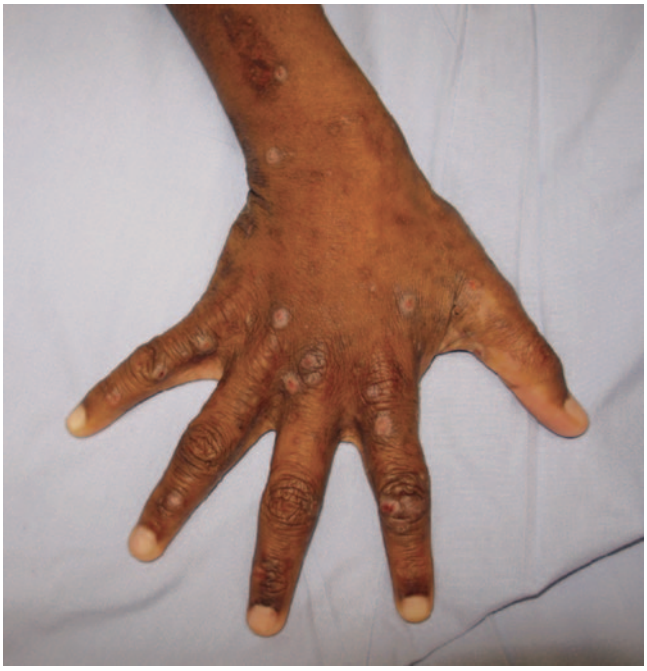

FIG. 2. Scabies of the hand with secondary infection.

(19) (Fig. 2). Sequelae include cellulitis, invasive bacterial infections, and APSGN. Scabies and skin infections in childhood have been linked with the extremely high rates of end-stage renal failure in indigenous adults.

Crusted Scabies

Crusted scabies was first described among leprosy patients in Norway in 1848 and thus is historically known as Norwegian scabies. It is a severe, debilitating disease characterized by large numbers of mites, high immunoglobulin E (IgE) levels, peripheral eosinophilia, and the development of hyperkeratotic skin crusts that may be either loose, scaly, and flaky or thick and adherent (Fig. 3). The distribution over the body can be localized or extensive and can include the neck, scalp, face, eyelids, and the area under the nails (Fig. 4). Crusts reveal large numbers of mites and eggs, totaling over a million in the most severe cases. Consequently, crusted scabies is considerably more infectious than ordinary scabies. People with crusted scabies have been recognized as "core-transmitters" (23, 29, 36) and as sources of reinfection following intervention programs (28). Patients with crusted scabies may also remain infectious for long periods of time because of the difficulty in eradicating mites from heavily crusted areas of the skin. Crusted scabies is caused by the same variety of mite that causes ordinary scabies. Progression from ordinary scabies to crusted scabies is uncommon, and susceptibility to the more severe form of the disease has been associated with a number of predisposing conditions. These include leprosy (Fig. 5), infection with human T-cell leukemia virus type 1 and human immunodeficiency virus, and immunosuppression by medication. However, crusted scabies can occur in overtly immunocompetent individuals, and some familial clustering suggests the possibility of a specific immune defect in these individuals

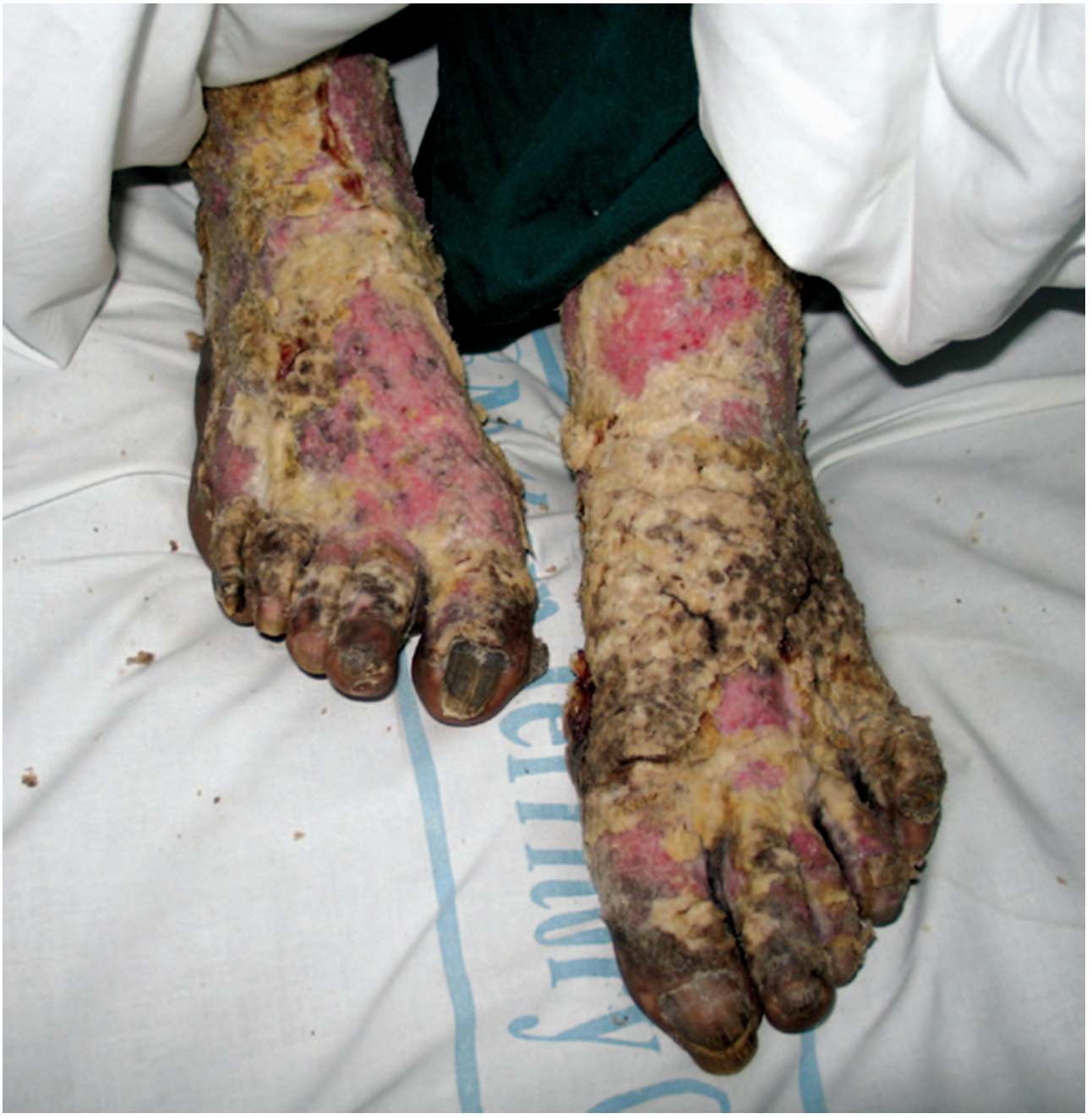

FIG. 3. Crusted scabies of the feet.

(97). Furthermore, the crusted scabies seen in former leprosy patients can occur long after infection has been treated and in the absence of sensory neuropathy. This has resulted in our hypothesis that the immune defect predisposing to clinical disease in leprosy may also predispose to hyperinfestation following *S. scabiei* infestation (66). Nevertheless, crusted scabies can also occasionally occur locally in a paralyzed limb or a limb with sensory neuropathy, presumably reflecting the absence of itch or the inability to scratch (23). Crusted scabies has also been observed in patients with cognitive deficiency and in institutionalized patients, seemingly because they are unable to properly interpret the associated pruritus or are unable to physically respond to the itching (67). Fissure development and secondary bacterial infections are common and are associated with the high mortality rates for this form of the disease (28) (Fig. 6A and B).

ANIMAL SCABIES

Worldwide, *S. scabiei* causes mange in many companion and livestock animals and is responsible for epizootic disease in wild populations of a number of animal species (89). Sarcoptic

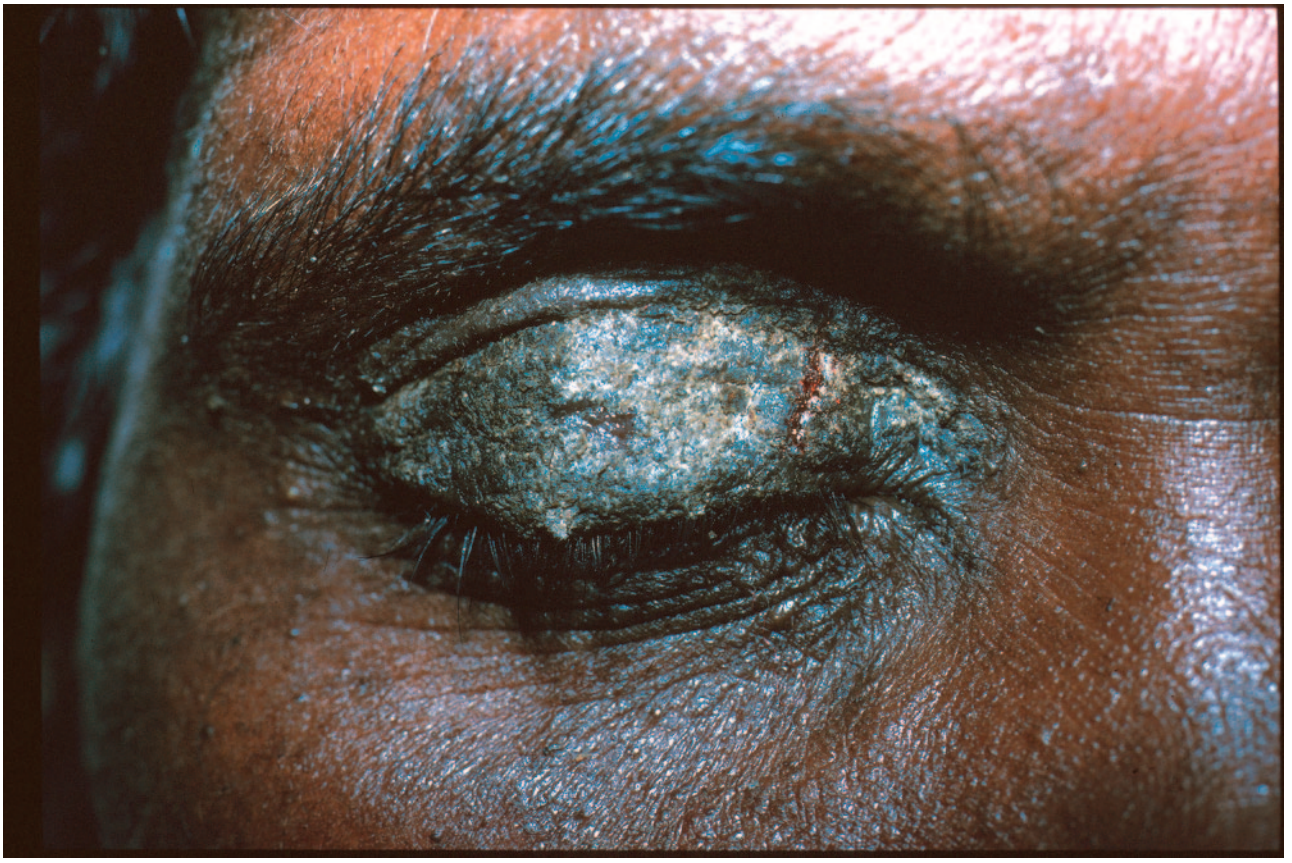

FIG. 4. Crusted scabies of the eyelid.

mange is considered a major cause of mortality among red foxes (*Vulpes vulpes*) (14), coyotes (90), and common wombats (*Vombatus ursinus) (*74). Veterinary concerns include difficulties in diagnosis and control and the economic effect of mange on feed conversion efficiency. In production herds, the intense pruritus associated with the disease interferes with milk production, weight gain, and leather quality and can inflict serious economic losses on primary industries (35, 95).

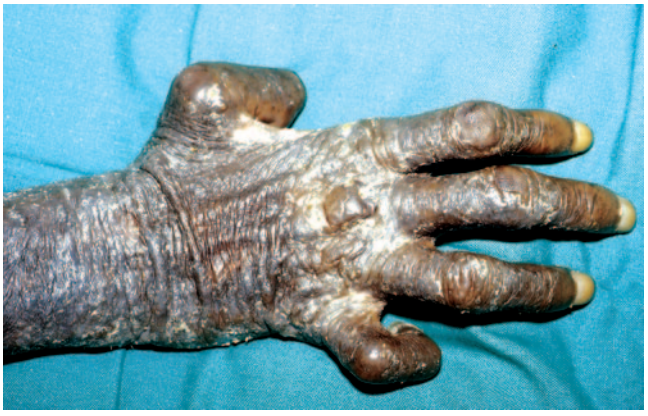

FIG. 5. Crusted scabies in a patient with leprosy.

Clinical Features of Mange

The clinical signs of mange in animals are slightly raised red papules seen on the sparsely haired regions of the body. Intense pruritus is evident, with consequent scratching, excoriation, and skin inflammation. If mange is left untreated, loss of hair, scaling, and crusting of the skin with dried exudate of serum are observed (Fig. 7). Secondary pyoderma may occur. Transmission of mites among a group of animals is most likely through direct contact or via contaminated bedding.

Host Specificity

Mite populations are primarily host specific, with little evidence of interbreeding between strains. Cross-infection studies describe unsuccessful experimental attempts to transfer scabies mites from dogs to mice, pigs, cattle, goats, and sheep (10). This is supported by molecular genotyping studies that reveal genetically distinct dog and human host-associated mite populations in Australian indigenous communities where scabies is endemic (106, 108). Occasional cases of human scabies have been reported following exposure to animal scabies, but these infestations are generally self-limiting, with no evidence of long-term reproduction occurring on the nonnormal host (15).

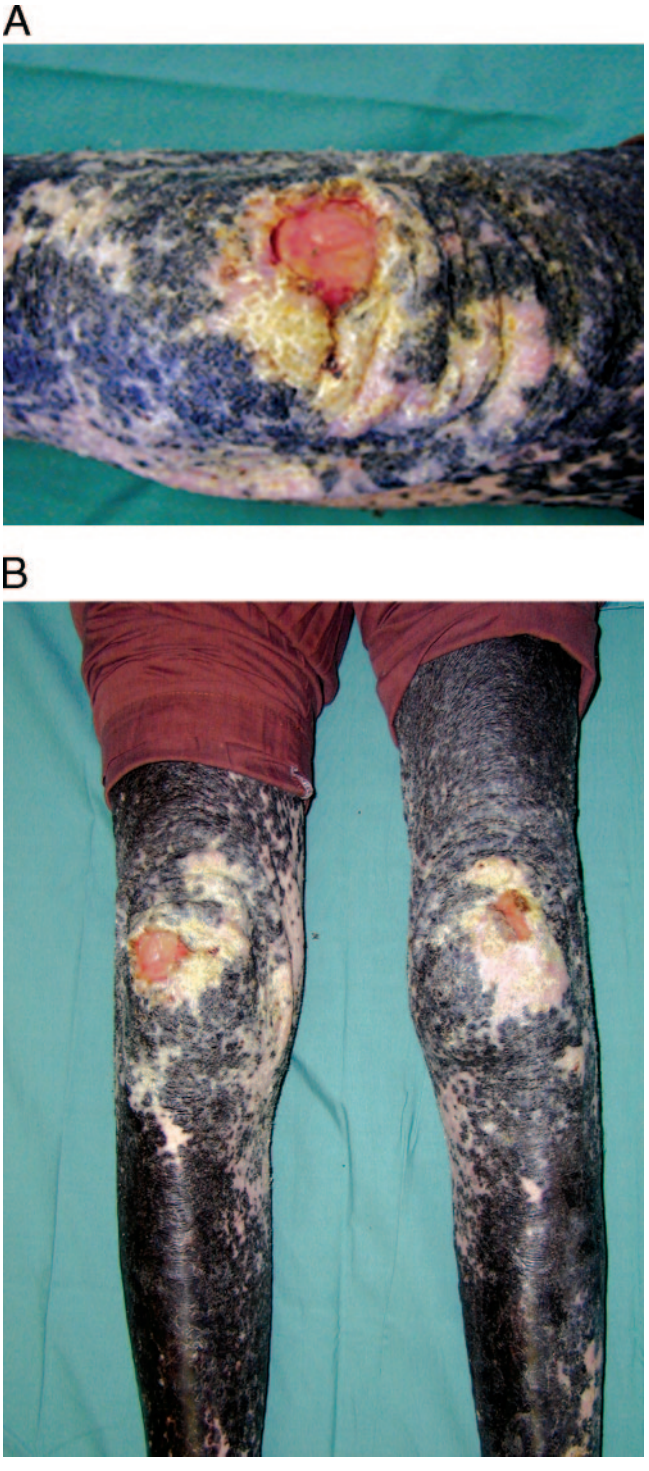

FIG. 6. Crusted scabies with chronic secondary ulcers and depigmentation.

FIG. 7. Crusts and alopecia in a dog with severe scabies.

HOST IMMUNE RESPONSE

Studies of the symptoms and signs of scabies pointed to the development of host immunity, but until the recent Scabies Gene Discovery Project (43), only a small number of the antigens responsible for the immune reactions to scabies had been sequenced and characterized (51, 75). Consequently, there is a dearth of literature reporting scabies-specific humoral or cellular immunity. Limited past investigations of humoral immunity in scabietic patients show contradictory results and have used whole-mite scabietic extracts from other hosts, such as dogs (82). Immunoblotting studies demonstrate that sera from crusted scabies patients showed strong IgE binding to up to 21 *S. scabiei* var. *canis* proteins (4). However, the identity of these allergens was unknown. Patients with crusted scabies are noted to have extremely high serum levels of total IgE and IgG (97). Cell-mediated host immune responses have been identified primarily by histopathological examination of skin biopsy specimens from scabietic lesions. Mite burrows are surrounded by inflammatory cell infiltrates comprising eosinophils, lymphocytes, and histiocytes (Fig. 8). Furthermore, biopsy specimens containing both mites and inflammatory papules have been observed to contain IgE deposits in vessel walls in the upper dermis (20). Unknown components in an extract of *S. scabiei* var. *canis* have been shown to influence cytokine expression in cultured human keratinocytes, fibroblasts, hu-

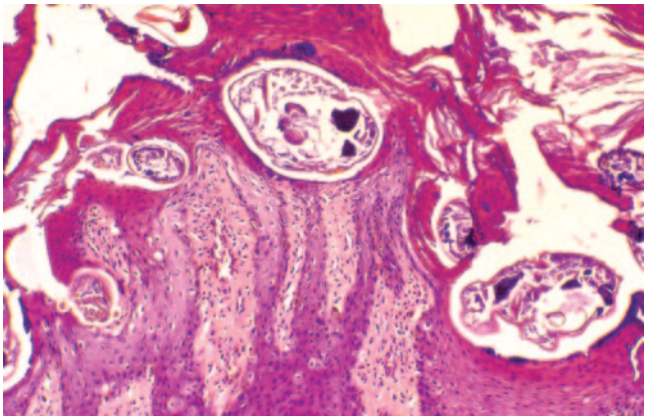

FIG. 8. Skin biopsy of crusted scabies showing mites in the epidermis with hyperkeratosis and inflammatory response.

man peripheral blood mononuclear cells, and dendritic cells (5–7). Current studies are investigating scabietic patients' antibody and cellular responses to specific recombinant *S. scabiei* var. *hominis* antigens. Results have identified patients with both crusted and ordinary scabies to have strong peripheral blood mononuclear cell proliferative responses and IgE antibody responses to multiple *S. scabiei* homologues to house dust mite allergens (Walton and Currie, unpublished). Scabies mite-inactivated serine protease paralogues have been identified both internally in the mite gut and externally in feces (114). Furthermore, human IgG has been identified in the guts of mites, which must presumably also contain the serine protease cascades of both the blood clotting and complement fixation pathways. Complement has been shown to be an important component in a host's defense against ticks (113). Both of these pathways must be inhibited while simultaneous digestion of epidermal protein as food takes place.

Immediate versus Delayed-Type Hypersensitivity Reactions to Scabies Mites

The severe itching and papular rash of the primary infestation are accompanied by skin lesions characterized by inflammatory cell infiltrates typical of a delayed sensitivity cell-mediated immune reaction. However, immediate wheal reactions have been elicited by intradermal injection of scabies mite extracts in both ordinary and crusted-scabies patients but not healthy volunteers (42, 105). This response was observed to wane with time, and patients injected 15 to 24 months after infestation did not react.

Cross-Reactivity between Scabies Mite Infections and House Dust Mite Allergy

Investigations have demonstrated that patients sensitive to house dust mites but with no history of scabies have circulating IgE antibodies that recognize antigens in *S. scabiei* var. *canis* extract (13). Furthermore, Western blot and radioallergosorbent assays demonstrated that individuals with scabies showed strong IgE binding to house dust mite extract (40). The specific cross-reactive molecules remain unidentified but may represent some polysaccharide-related IgE cross-reactivity (71). Scabies mites and house dust mites are phylogenetically related arthropods, and it is not surprising that they or their excretions or secretions have homologous allergens. However, it is unknown how many of these will be cross-reactive or what the clinical significance of any such cross-reactivity is. For example, studies on cross-reactivity between the group 5 allergens of house dust mites *Dermatophagoides pteronyssinus* and *Blomia tropicalis* (Der p 5 and Blo t 5) have been undertaken, and although they have 43% amino acid identity, they have been found not to be cross-reactive (68).

TREATMENT

There are a number of agents available on the market to treat scabies, and choice is largely based on the age of the patient, state of their health, degree of excoriation or eczema, potential toxicity, cost, and availability. For instance, previously, lindane (gammabenzene hexachloride) was the topical agent most commonly recommended for treatment of scabies in Western countries. However, because of potential neurotoxicity, it has now been removed from the market in Australia and much of Europe. Five percent permethrin is now the most frequently prescribed topical treatment in affluent countries, but its cost precludes its use in many regions where scabies is endemic. Topical application of active substances is the primary means of effective treatment, although oral ivermectin is increasingly used and is now registered for scabies treatment in France (25, 98). In situations where scabies is endemic, empirical treatment is often more cost-effective than attempting laboratory-based diagnoses. Intervention programs in Panama, Brazil, the Solomon Islands, and remote northern Australian Aboriginal communities have resulted in dramatic reductions in the prevalence of scabies and skin sores (58, 103, 116). These programs involve either mass topical treatment of community members with 5% permethrin or administration of oral ivermectin, with different models adapted to local conditions. Success at the individual community level has varied and has not always been sustainable. Often low levels of scabies persist within communities after the implementation of these community-based programs (115). Furthermore, mass community treatment in communities of endemicity creates an environment for emerging drug tolerance or resistance, and new approaches to control are needed. Published in vitro acaricide efficacy studies indicate that *S. scabiei* mites in northern Australia are becoming increasingly tolerant to 5% permethrin (111), and clinical and in vitro ivermectin resistance in cases of scabies has recently been documented (31). Resistance should also be considered in regions of nonendemicity when patients experience persistent symptoms for up to several weeks after curative treatment. Promising new acaricides include a number of essential oils in which terpenoids are most likely the primary active components (110). Encouraging in vitro and field results have been obtained for 5% tea tree oil extracted from the tree *Melaleuca alternifolia* (110, 111), 20% lippia oil extracted from *Lippia multiflora* Moldenke (86), a paste made from neem (*Azadirachta indica* ADR) and turmeric (*Curcuma longa*) (24), camphor oil (*Eucalyptus globulus*) (83), and a commercially available repellent containing coconut and jojoba oil (55). In regions in which the prevalence of scabies among children is between 5 and 10%, it is important to be able to counteract epidemics of scabies with effective treatments and a sensitive and specific tool able to determine both clinical and subclinical infestations. In the treatment of crusted scabies, the importance of combining topical therapy with oral ivermectin has been noted (77). Severe crusted-scabies cases may require up to seven doses of ivermectin to ensure the cure and eradication of mites (64, 97).

DIAGNOSTIC TECHNIQUES

Clinical Diagnosis

Currently there is no efficient means of diagnosing human or animal scabies. To date, diagnosis is via clinical signs and microscopic examination of skin scrapings, but experience has shown that the sensitivity of these traditional tests is less than 50%. Detecting visible lesions can be difficult, as they are often obscured by eczema or impetigo or are atypical. Detection of

burrows with India ink was advocated more than 20 years ago (117), but the test is often impractical and is not routinely used. Presumptive diagnosis can be made on the basis of a typical history of pruritus, pruritus that is worse at night, the distribution of the inflammatory papules, and a history of contact with other scabies cases (76).

Microscopy

Definitive diagnosis is based on the identification of mites, eggs, eggshell fragments, or mite fecal pellets from skin scrapings (e.g., from scabietic papules or from under the fingernails) or by the detection of the mite at the end of its burrow. One or two drops of mineral oil are applied to the lesion, which is then scraped or shaved, and the specimens are examined after clearing in 10% KOH with a light microscope under low power. This method provides excellent specificity but has low sensitivity for ordinary scabies, due to the low numbers of parasites. Furthermore, several factors may influence the level of sensitivity, e.g., the clinical presentation (unscratched lesions are more valuable), the number of sites sampled and/or repeated scrapings, and the sampler's experience. A skin biopsy may confirm the diagnosis of scabies if a mite or parts of it can be identified. However, in most cases, the histological appearance is that of nonspecific, delayed hypersensitivity with superficial and deep perivascular inflammatory mononuclear cell infiltrates with numerous eosinophils, papillary edema, and epidermal spongiosis (41). In practice, identifying a mite is challenging, and a negative result, even from an expert, does not rule out scabies. Presumptive therapy can be used as a diagnosis, but its value is questionable and confounded by the variable delay until resolution of symptoms following therapy. A positive response to treatment cannot exclude the spontaneous disappearance of a dermatological disease other than scabies, and a negative response does not exclude scabies, especially with resistant mites (25). In the absence of confirmed mites, diagnosis is currently based entirely on clinical and epidemiological findings. Given the extensive differential diagnoses, the specificity of clinical diagnosis is poor, especially for those inexperienced regarding scabies. Furthermore, there are the difficulties in distinguishing among active infestation, residual skin reaction, and reinfestation.

Dermatoscopy

Epiluminescence microscopy and high-resolution videodermatoscopy are noninvasive techniques that allow detailed inspection of the patient's skin, from the surface to the superficial papillary dermis (2, 49, 80). Diagnosis is by observations of the "jet-with-contrail" pattern in the skin representing a mite and its burrow. Due to difficulties obtaining skin scrapings from some patients, e.g., infants, and the lack of sensitivity of classical methods, dermatoscopy might be informative (49), but studies performed on large cohorts are lacking (25) and limited by the high cost of the equipment.

Antigen Detection and PCR Diagnostic

The key weakness of a scabies PCR diagnostic is that, as with microscopy diagnosis, it relies on the physical presence of a mite or mite part in the sample. Therefore, it is unlikely to become a viable test for widespread use, due to the generally low mite burden and, thus, low sensitivity. PCR followed by enzyme-linked immunosorbent assay detection of the PCR product was suggested to be a sensitive technique for diagnosing patients with atypical scabies (16). However, the method described was labor-intensive and time-consuming.

Intradermal Skin Test for Scabies

The intradermal skin test method is currently not feasible to use with whole-mite extract due to the inability to culture sufficient quantities of *S. scabiei*. Furthermore, whole-mite extracts obtained from animal models contain a heterogenous mixture of host and parasite antigens, including house dust mite cross-reactive epitopes, and vary in composition, potency, and purity. Patients with scabies often present to clinicians with a generalized pruritus of unknown cause. Purified, well-characterized recombinant scabies mite allergens with standardized protein contents could potentially be utilized in the future for scabies skin test assays for clinically difficult-to-diagnose cases and for immunotherapy.

Antibody Detection

Studies document that scabies mite infestation causes the production of measurable antibodies in infested host species (4, 40). Furthermore, host IgG has been demonstrated in the anterior midgut and esophagus of fresh mites (94, 114). Enzyme-linked immunosorbent assays have now been developed for the detection of antibodies to *S. scabiei* in pigs and dogs and are commercially available in Europe (17, 18, 59). These assays rely on whole-mite antigen preparations derived from *S. scabiei* var. *suis* and the itch-mite of the red fox, *S. scabiei* var. *vulpes*, and therefore have limitations in availability and specificity. Importantly, a recent study looking at cross-reacting IgG antibodies to the fox mite antigen in human scabies reported a sensitivity of only 48%, in comparison with 80% in pig scabies and 84% in dog scabies (50). This is not surprising, as studies using molecular markers suggest that *S. scabiei* organisms from humans and animals are genetically distinct and that interbreeding or cross-infection appears to be extremely rare (106, 108).

S. SCABIEI GENE DISCOVERY

A major limitation in biomedical research on scabies has been the difficulty of obtaining mites in sufficient numbers, due to the generally low parasite burden and the lack of an in vitro culture system. To overcome this, cDNA libraries have now been constructed from *S. scabiei* var. *hominis* and *S. scabiei* var. *vulpes* (43, 44, 70), and large expressed sequence tag databases containing both partial and complete DNA sequences of *S. scabiei* genes have been established. From these databases, scabies mite homologues to most of the known house dust mite allergens have now been identified, as well as many other relevant molecules (33, 43, 61, 62, 75, 91). Recombinant antigens promise a continuous, reproducible quantity of allergenic proteins in a purified form suitable for use in in vitro assays.

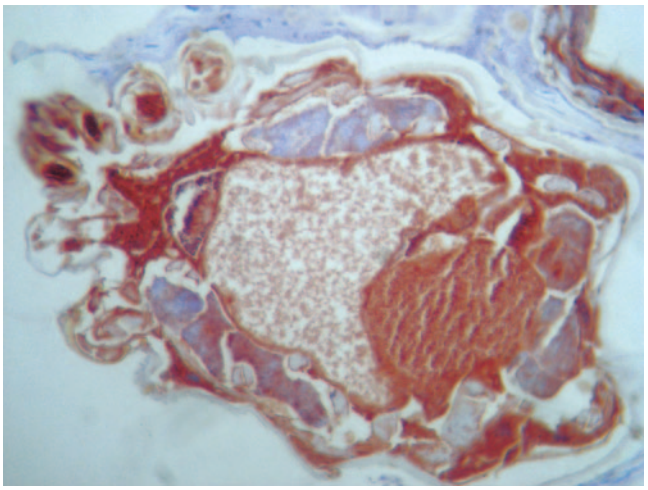

FIG. 9. Serial section of human scabies mite. Red shows binding of polyclonal *S. scabiei* anti-group 8 antibodies raised in rabbits to protein in vivo. (Courtesy of C. Willis, Queensland Institute of Medical Research, Brisbane, Queensland, Australia.)

Immunodiagnostic Assay Using Recombinant *S. scabiei* Allergens

Recently, a number of scabies mite homologues to house dust mite allergens have been cloned, expressed, and affinity purified. These include mature forms of both active and inactive homologues of the cysteine protease group 1 allergens (62), mature forms of active and inactive homologues of the serine protease group 3 allergens (61), a mu class and a delta class glutathione *S*-transferase group 8 allergen (33, 91), and a homologue to the C terminus of an apolipoprotein group 14 allergen (51). Immunohistochemical staining of sections of human skin which was highly infested with *S. scabiei* mites showed that anti-group 8 and anti-group 14 antibodies (generated in mice and rabbits, respectively) localized to the internal organs of the scabies mites and the cuticle, with minor staining in the digestive system (51) (Fig. 9). Moreover, the group 1 and group 3 scabies mite allergens have now been expressed in *Pichia pastoris*, with considerable evidence that they are in native conformation and that they are localized to the digestive system of the mite (114; D. Kemp and K. Fischer, personal communication). Studies are now under way to evaluate the diagnostic potential of the identified proteins by characterizing specific human and animal humoral and cellular immune responses. Serological features that are diagnostically important are the interval between exposure to infection and antibody response and the nature of the antibodies that make up the response.

CONCLUSIONS

Using an appropriate recombinant antigen, the development of an *S. scabiei* immunodiagnostic assay is now a real possibility. Its development will enable the selective treatment of affected individuals and animals, reducing the requirement for mass treatment and the associated costs. This should decrease the potential for escalating mite resistance and provide another means of controlling scabies in highly affected areas. There is little evidence that simple mass treatment is effective in the long term. Molecular studies aimed at improved diagnosis and better therapeutic options will significantly contribute to reductions in the high prevalence of scabies observed currently in resource-poor communities.

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